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Case Report

Very late stent thrombosis after drug-eluting stent implantation in a patient with antiphospholipid syndrome

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KEYWORDS
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Summary A 74-year-old woman was admitted to our hospital with chest pain and shortness of breath. Coronary arteriograms revealed occlusion of a drug-eluting stent, which had been implanted 33 months earlier, in the middle right coronary artery. During percutaneous coronary intervention, distal embolization developed and a thrombus was detected with an aspiration catheter. Serological examinations performed 1 year before and during the present hospitalization revealed positive lupus anticoagulant activity. Thrombophilic tendencies, such as antiphospholipid syndrome, are noteworthy as one of the causative factors in very late stent thrombosis.

Introduction

It has been recently demonstrated that stent thrombosis may occur more than a year after implantation of a drug-eluting stent (DES). It has also been reported that discontinuation of antiplatelet therapy and procedural and lesion-related variables, such as stent underexpansion, stent length, and multivessel disease, are risk factors for stent thrombosis. Among patient-related variables, diabetes mellitus and renal failure have been mentioned as risk factors [1]. However, despite being a thrombotic complication, thrombophilic tendencies are discussed in few reports. Here we present a case of very late stent thrombosis after implantation of DESs in a patient with antiphospholipid syndrome (APS).

Case report

A 74-year-old woman was admitted to our hospital with chest pain and shortness of breath, which had developed 2 weeks earlier. She had undergone percutaneous coronary intervention 33 months before the present hospitalization for effort angina. Sirolimus-eluting stents had been successfully implanted in the middle and distal right coronary artery (segments 2 and 3 in Fig. 1). Four months after

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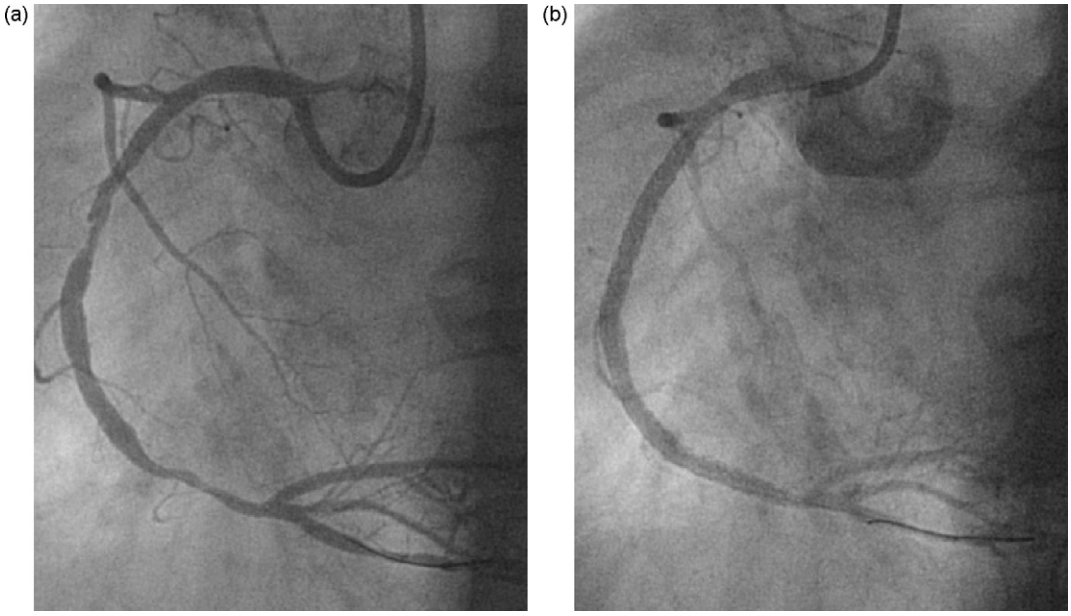

Figure 1 Coronary arteriograms obtained 33 months before stent thrombosis. Severe stenosis can be seen at segments 2 and 3 of the right coronary artery (a), and successful implantation of sirolimus-eluting stents has been accomplished (b).

stenting, coronary arteriograms showed no restenosis. One year before the present hospitalization, she had visited the outpatient department of neurology in our hospital because of dizziness. Prolonged activated partial thromboplastin time, positive lupus anticoagulant activity, and lacunar stroke had been detected.

Routine hematological and blood chemistry tests on admission, including platelet count, were normal. Left coronary arteriograms did not show stenosis but showed collateral circulation to the right coronary artery with no filling defect of the contrast medium in the stent implanted at segment 3 (Fig. 2a). The right coronary arteriogram revealed an in-stent obstruction at segment 2 (Fig. 2b).

Dual antiplatelet therapy consisting of aspirin (81 mg/day) and ticlopidine (200 mg/day) was continued after stenting. As mentioned above, lupus anticoagulant was detected 1 year previously and serological examination revealed positive lupus anticoagulant activity again (67.5 s) (Table 1). The activated partial thromboplastin time was measured using Thrombocheck APTT-SLA (Sysmex Corporation, Kobe, Japan). The presence of lupus anticoagulant was confirmed from the difference between the coagulation time after addition of normal plasma and that after addition of excess phospholipid by the phospholipid neutralization assay using STACLOT L.A. (BML. Inc. Tokyo, Japan).

Warfarin was then added to the dual antiplatelet therapy, and the patient underwent coronary intervention 5 days after routine coronary catheterization. The lesion was easily crossed using a floppy guide-wire and a balloon. However, after balloon deflation, a right distal coronary arteriogram, obtained through a micro catheter inserted deeply into the right coronary artery, revealed a filling defect in the

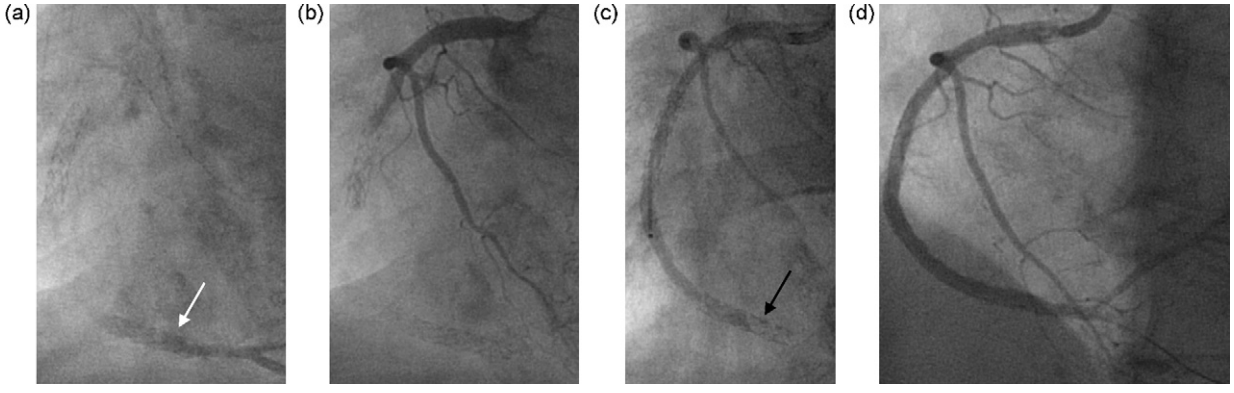

Figure 2 Retrograde right coronary arteriogram through collateral vessels from the left coronary artery shows no filling defect of the contrast medium in the stent implanted at segment 3 (white arrow in panel a). The right coronary arteriogram reveals obstruction in the stent implanted at segment 2 (b). After balloon dilation, the right coronary arteriogram shows distal embolization which is recognized as a filling defect in the stent implanted at segment 3 (black arrow in panel c). (d) The final arteriogram after aspiration therapy of the thrombus.

Table 1 Results of serological tests.

	Reference values	One year earlier	Day 3
C3	80—140 mg/dl		120
C4	11—34 mg/dl		40.8
CH50	30—45 U/ml		60
Anti-nuclear antibody	0—79		<40
Protein C	70—150%		129
Protein C activity	70—140%		131
Protein S	65—135%		95
Anti-CL.β2GP1 antibody	∼3.5 U/ml	1.7	
IgG anticardiolipin antibody	∼10 U/ml		9
Lupus anticoagulants	0—7.9 s	78.4	67.5
PT (s)	10—12 s		
PT (%)	70—150%	120	
APTT (s)	25—35 s	60.5	
APTT (%)	70—150%	43	
Fib	200—400 mg/dl	236	

stent implanted at segment 3 (Fig. 2c). This filling defect had not been recognized in the retrograde arteriogram obtained through the collateral circulation at routine coronary catheterization. We confirmed the presence of a thrombus using an aspiration catheter and diagnosed drifting of the thrombus which occluded segment 2 resulting in embolization at segment 3. There was no stent fracture, and incomplete stent apposition was not detected by intravascular ultrasonography. The atrioventricular node artery was reperfused but the posterior descending artery remained occluded after aspiration of the thrombus and administration of isosorbide dinitrate, nicorandil, and verapamil hydrochloride (Fig. 2d). However, there was a collateral circulation from the left coronary artery to the posterior descending artery, and hence, partial resolution of ST elevation was noted and coronary intervention came to an end. The clinical course was good and recurrence of stent thrombosis was not recognized. The patient was discharged on day 11.

Discussion

Late stent thrombosis after DES implantation has recently received a great deal of attention. In general, risk factors for stent thrombosis include discontinuation of antiplatelet therapy and procedure-related variables such as stent underexpansion, stent length, and the presence of multivessel disease. Incomplete endothelialization, hypersensitivity reactions to DES polymer, and incomplete stent apposition have also been mentioned as pathological factors [1].

Among clinical variables, diabetes mellitus and renal failure are generally suggested as risk factors. However, there are few reports concerning thrombophilic tendencies in relation to stent thrombosis. Acar et al. [2] reported a case of acute stent thrombosis related to the deficiency of protein C and protein S. Turgut et al. [3] described a case of stent thrombosis 48 h after bare-metal stent implantation associated with essential thrombocythemia.

APS [4] is characterized by the presence of antiphospholipid antibodies (aPL), such as lupus anticoagulant (LA), anticardiolipin antibody (aCL), and anti-β_2 glycoprotein I antibody, along with at least one clinical manifestation, such as arterial or venous thrombosis, or complications related to pregnancy. Cerebral and myocardial infarctions are common in patients with arterial thrombosis, which occurs less frequently than venous thrombosis. Several mechanisms have been proposed to explain the prothrombotic condition in APS, including inhibition of protein C activation, inhibition of antithrombin, activation of platelets, interaction with endothelial cells resulting in tissue factor upregulation, and activation of the complement pathway by aPL.

In the Antiphospholipid Antibodies and Stroke Study (APASS) [5], 1770 patients who had experienced an ischemic stroke within 30 days were classified as positive or negative for aPL (either LA or aCL). The presence of aPL was not associated with subsequent vascular occlusive events over 2 years. However, a small subgroup in this study suggested that those who test positive for both LA and aCL antibodies tend to have a higher event rate. Zuckerman et al. [6] found a high level of aCL in 17 (14%) of 124 patients with acute myocardial infarction (aged 65 years or younger) on admission, and with the exception of one case, these levels persisted 3 months after the infarction. They concluded that the presence of aCL was a marker for a high risk of recurrence of coronary and thromboembolic events. Greco et al. [7] reported that 86 (37%) of 232 patients with chest pain syndromes and acute coronary events were positive for one or more aPL, and the presence of aPL was associated with the subsequent clinical course. They also reported that a family history of APS-related events was frequently associated with aPL positivity in patients. Serological tests, including aPLs, might be needed before percutaneous coronary intervention in such cases.

There have been reports of cases in which stents were successfully placed in patients with APS presenting with acute myocardial infarction or angina pectoris [8,9]. However, stent thrombosis occurred in some cases [10—14]. Ito et al. [10] reported a case of acute myocardial infarction concurrent with primary antiphospholipid syndrome, in which stent thrombosis occurred after emergency bare-metal stenting. After a routine catheterization with intravascular

ultrasound examination, thrombosis recurred in the chronic phase. Su et al. [11] described acute stent thrombosis after elective stenting in a patient with angina pectoris accompanied by APS. Muir et al. [12] also reported a case of recurrent acute stent thrombosis in APS secondary to renal cell carcinoma. Kyoi et al. [13] described a case of APS with very late stent thrombosis 7 years after bare-metal stent implantation. They indicated that multiple factors, such as discontinuation of antiplatelet therapy and dehydration induced by exercise, overlapped with disturbed re-endothelialization or malposition due to certain pre-existing causes, promoted the thrombogenicity in APS.

There are few reports of stent thrombosis after DES implantation in APS. Weissman and Coplan [14] described recurrent acute stent thrombosis after coronary intervention. In their case, coronary artery bypass graft surgery was eventually required. To our knowledge, there is no report of very late stent thrombosis after DES implantation in a patient with APS.

In the present case we diagnosed the patient as having APS because she suffered lacunar stroke and very late stent thrombosis, and had positive lupus anticoagulant activity that was measured 1 year before and during this hospitalization. Although this patient had a prothrombotic condition concurrent with APS, the trigger for stent thrombosis was unknown. Dual antiplatelet therapy was continued and there was no evidence of dehydration, infectious disease, or injury. There was no stent fracture, and incomplete stent apposition was not detected by intravascular ultrasonography. However, the presence of a thrombus was clear from the occurrence of distal embolization as well as from aspirated materials. Other factors such as chronic local inflammation may have gradually promoted APS thrombogenicity and an occluded thrombus might have been formed in the absence of myocardial infarction.

Standard oral treatment after PCI in patients with APS has not been established. In the APASS [5], there was no differential response to warfarin and aspirin therapy. However, in the present case, because the thrombotic occlusion occurred despite continuation of dual antiplatelet therapy, we considered that warfarin was needed in addition to dual antiplatelet therapy.

In conclusion, very late stent thrombosis may be associated with multiple factors. Thrombophilic tendencies such as APS should be considered as one of the causative factors of stent thrombosis.

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